REMARKS

Applicants have amended claims 9, 11, 12, and 14, cancelled claims 7 and 17, and added new claims 18-21. Applicants submit that the amendments to claims 9, 11, 12, and 14 and the addition of claims 18-21 do not introduce new matter, since the subject matter claimed was inherent in the claims as filed and/or is described in the specification. Specifically, the amendments and new claims are supported in the specification in Example III.

Claim Rejections

The Examiner has rejected claims 7, 9, 11, 12, 14, and 17 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants traverse.

Rejection of claims 11 and 12 under U.S.C. § 112, first paragraph

In the Advisory Action of October 29, 2003, the Examiner states that Applicants' arguments regarding the patentability of claims 11 and 12 were not persuasive. The Examiner contends that "there is no support for Applicants' assertion that BMP-9-induced upregulation of the genes associated with the cholinergic phenotype would necessarily translate into a prediction that BMP-9 would upregulate these genes in adult mouse and human tissue." (Advisory Action, at pp. 2-3.) Applicants disagree.

When establishing the state of the art, the Examiner must consider the evidence as a whole. Manual of Patent Examining Procedure, Section 2164.05. The MPEP further states that the evidence "need not be conclusive but merely convincing to one skilled in the art." Id. In responses filed January 2, 2003 and September 11, 2003, Applicants supplied the Examiner with a total of nine references describing the state of the art of delivery of neurotrophic factors to the nervous system. A selected group of

these references is enclosed for the Examiner's convenience, and descriptions of their teachings are set forth below. Generally, these references describe the use of a number of neurotrophic factors to induce or maintain various phenotypes in neurons and neuronal tissue *in vivo*. When taken as a whole, and using the "convincing" standard, these references establish that one skilled in the art would reasonably expect the function of a neurotrophic factor in a model system to correlate with a similar function in the brain or nervous system of a patient.

1) Tuszynski, (2000) *Cell Transplantation* 9:629-636, discloses that nerve growth factor (NGF), originally shown to influence cholinergic innervation of the embryonic hippocampus during development, functions to rescue degenerating cholinergic neurons and increase choline acetyltransferase expression after administration to the brain in adult mice.
2) Walton et al., (1998) *Pharmaceutical Research* 15(3):377-385, discloses that glial cell line-derived neurotrophic factor (GDNF), originally shown to promote dopamine uptake in embryonic mesencephalic cultures, can be administered to patients to support the survival of neurons *in vivo*.
3) Klein et al., (2000) *Brain Res* 875:144-151, discloses the delivery of NGF in a virus vector increases cholinergic neuron size and prevents memory loss in adult mice.
4) Jonhagen et al. (1998) *Dement Cogn Disord* 9:246-257, discloses clinical trials showing that the intracerebroventricular administration of NGF to patients produced improvement in a number of neuropsychology tests.
5) Nabeshima et al. (2000) *Alz Dis and Assoc Disord* 14(Supp 1):S39-S46, discloses that the delivery of NGF to the brain prevented cholinergic neuron atrophy in rats:

6) Wang et al. (2001) *Stroke* 32:2170-2178, discloses that BMP-6, originally shown to be a general growth inductive factor, augments dopamine neuron survival in mice.

In addition to the previously cited references, Applicants submit Liu et al., (2001) *Brain Res* 905:81-90, which discloses that BMP-7, originally shown to promote dendritic growth in cultured neurons, enhanced recovery of sensory and motor neuron function in a mouse stroke model.

Taking the teachings of these references as a whole, one skilled in the art would reasonably predict that a neurotrophic factor shown to upregulate certain genes in development, such as BMP-9, will also upregulate those same genes when administered to adult animals. The specification clearly demonstrates that the delivery of BMP-9 to neuronal cells induces and maintains the expression of choline acetyltranserase and vesicular acetylcholine tranporter (Examples III-VII). Claims 11 and 12 specifically recite the induction of the expression of these genes. Accordingly, Applicants submit that given Applicants' disclosure, the state of the art at the time of filing was such that one skilled in the art would reasonably expect there to be a correlation between the function of BMP-9 in embryos and its ability to induce the expression of choline acetyltranserase and vesicular acetylcholine transporter in adults.

The Examiner also contends that "one skilled in the art would not expect that upregulation of genes within existing neurons would be sufficient to replace the connections lost by cholinergic neurons that have already degenerated." (Advisory Action, at p. 3) Again, Applicants disagree. When BMP-9 is administered to the brain of a patient, it will increase the expression of neurotransmitters like choline acetyltransferase and vesicular acetylcholine transporter. This upregulation will at least

partially replace the lost production of these same neurotransmitters caused by a degeneration of cholinergic neurons. The claims as written do not require total replacement of the functions of the degenerating neurons. Furthermore, it is not necessary for BMP-9 to actually replace neural connections, but only to replace the lost production of neurotransmitters. Therefore, Applicants have sufficiently disclosed how to use the invention of claims 11 and 12. In light of the above arguments, Applicants submit that claims 11 and 12 are enabled by the specification and any rejection of these claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejection of claims 7, 9, 12, 14, and 17 under U.S.C. § 112, first paragraph

In the Advisory Action of October 29, 2003, the Examiner contends that Applicants' arguments regarding the patentability of claims 7, 9, 12, 14, and 17 are limited to the assertion that administration of BMP-9 can induce upregulation of the genes associated with the cholinergic phenotype rather than the differentiation of cholinergic neurons. Claims 9 and 17 have been cancelled. Amended claims 7, 12, and 14, as well as new claims 18-21, now recite the use of BMP-9 to treat patients by increasing the levels of choline acetyltransferase and vesicular acetylcholine transporter in patients with degenerating or malfunctioning neurons, rather than inducing the differentiation of cholinergic neurons. Applicants submit that these claim amendments overcome the Examiner's concern that "the specification does not provide specific guidance with regard to the location of neuronal progenitor cells within the adult brain, such that one of skill in the art could reasonably expect these newly generated cholinergic neurons to integrate into a functioning neural network." In the amended claims, the only functional requirement is that BMP-9 increases the levels of choline

acetyltransferase and vesicular acetylcholine transporter in the nervous system of the patient. The amendments to claims 7, 12, and 14 overcome the Examiner's rejection of these claims, as well as any potential rejection of new claims 18-21. Applicants respectfully request that the rejection of claims 7, 12, and 14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of claims 9 and 17 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 9 and 17 as indefinite under 35 U.S.C. § 112, second paragraph. The Examiner contends that the phrase "method for treating degenerating cholinergic neurons in a patient" in claim 9 is indefinite because no treatment of these neurons is achieved. The Examiner also contends that the phrase "method for treating malfunctioning cholinergic neurons in a patient" in claim 17 is indefinite because no treatment of these neurons is achieved. Claims 9 and 17 have been cancelled. However, to avoid similar rejections of new claims 18-21, these claims recite "method for treating a patient" as opposed to "method for treating neurons." Applicants submit that these changes overcome the rejection under 35 U.S.C. § 112, second paragraph, and request that claims 18-21 be allowed.

In view of the foregoing amendments and remarks, Applicants request the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any additional extensions of time required to enter this response and charge any required fee to Deposit Account 06-0916.

Respectfully submitted,

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